Remarks

The present Reply with Amendment is believed to address remaining issues and hopefully place the application in condition for allowance. Applicant has the following remarks concerning the pending rejections and how they have been further addressed by the present paper.

It is believed that replacement copies of all missing IDS references have been provided (which have apparently gone missing from the file of the immediate parent application). The Examiner is requested to contact the undersigned if any references are still missing or are illegible.

Applicant has not amended the "Brief Description of the Drawings" Section as requested since, upon inspection thereof, it reasonably appears that each brief description, as originally submitted, immediately and fully explains to the reader that each Figure is a multipanel drawing. Applicant respectfully believes that the administrative burden caused by generating the replacement paragraphs is not worth the trouble, under the current rules for entry of amendments.

The Examiner has noted several instances where website identification /hyperlinks have been included in the Specification. Each such instance has been simply removed, which is sufficient.

Applicant has provided the requested amendments to Claims 26 and 55 to overcome the stated objections as to formalities.

In regard of the rejection of the claims under 35 USC section 112, first paragraph, it so happens that the monoclonal antibodies in question are well known commercial reagents readily available in commerce, and the Specification has been amended to indicate both the source and well known long term availability of these reagents.

In regard of Claims 28, 38, 41, 42, and 43, it is believed that all of the rejections under section 112, second paragraph have been addressed by appropriate amendments.

Since the Examiner has already indicated the presence of allowable subject matter, Applicant respectfully requests that the Examiner contact the undersigned to hopefully conclude remaining matters.

Applicant again notes that the present patent application represents a major and pioneering medical advance, i.e. the recognition that previously hoped for "gene therapy" approaches to p53 therapy can be surprisingly replaced by small molecule approaches. The present invention is accordingly reflected in the much cited publication, Science, v. 286, pp. 2507-2510, which is of record herein).

By way of a Supplemental Information Disclosure Statement submitted herewith, Applicant respectfully directs attention to M. Demma et al., "CP-31398 Restores DNA Binding Activity to Mutant p53 in vitro but Does not Affect p53 Homologs p63 and p73", J. Biol. Chem. v. 279, pp. 45887-45896, 2004 Internet published on August 11, 2004 as

manuscript M401854200.

All of the authors of this publication are employees of Schering-Plough Corporation, a pharmaceutical company that has for many years embraced the gene therapy approach to p53 therapy. It is remarkable that upon reading the present Applicant's publication in Science, Applicant's competitor immediately and extensively validated the present invention and its applicability to drug discovery. It should be noted that "CP-31398" as used in the title of the Schering-Plough publication is Applicant (i.e. Pfizer)'s very own compound identifier, and corresponds exactly to the highly effective compound X that was screened according to the very teachings of the present Specification.

In this regard, attention is again directed to Page 12 of the present application referring to Figure 6, showing testing of compound "X", N-{2-[2-(4-Methoxy-phenyl)-vinyl]-quinazolin-4-yl}-N',N'-dimethyl-propane-1,3-diamine hydrochloride. The species referred to as compound "X" is depicted in Figure 2 of the Specification, and is also the subject of *in vivo* model Example 4 (pages 49-50), and Figures 5 and 6 (see pages 11-12). Compound X of the present application **is** "CP-31398".

Attention is also directed to C. Rao et al., Abstract 2244 from the American Association for Cancer Research, 2004, reflecting studies independently sponsored from the National Cancer Institute, Bethesda, MD validating the ability of Compound X (CP-31398) to both rescue destabilized mutant p53 and promote the activity of wild-type p53. Still additional validating support for the activity of Compound X, and therefore the methodology of the present invention, is provided by the additional journal publications (also attached) of P. Stanhope-Baker et al., and J. Wischhusen et al. (which includes the Applicant herein as author). It is thus clearly apparent that those skilled in the art have recognized that the teachings of the present invention are directed to valuable medical technology which has now been embraced for the very purpose taught by the claims solicited herein, for the discovery of chemical compounds that can correct defective p53 under physiological conditions in patients.

Conclusion

An early and favorable reply is respectfully requested. The Examiner is requested to contact the undersigned so that a telephonic interview can be conducted. No fee (other than for the Supplemental IDS) is due in connection with this supplemental submission.

Respectfully submitted,

Date: 3/17/2005

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Marked Up Version of Amended Paragraphs

Paragraph replaced on Pages 13-14

According to the practice of the invention, a protein of the p53 family is defined as a mammalian p53, p63, or p73; and/or a protein that possesses a domain, all having at least 50%, more preferably 80%, of amino acid sequence homology to one or more of (1) the N-terminal domain required for transcriptional activation, (2) the DNA-binding domain, or (3) the oligomerization domain of a mammalian p53, p63, or p73, wherein said homology is measured by any of the recognized algorithms BLASTP v. 2.0 [(www.ncbi.nlm.nih.gov)] (Alschul et al., 1990, J. of Molec. Biol., 215:403-410, "The BLAST Algorithm; Altschul et al., 1997, Nuc. Acids Res. 25:3389-3402) and W.U.-BLAST-2.0 (available from Washington University, St. Louis, MO, USA), and wherein said protein evidences at least one function that is recognized in the art as characteristic also of p52, p63, or p73 (e.g. for example, capability of activating p53 responsive promoters and induce apoptosis; for discussion of art-recognized properties, see Kaelin, 1999; Yang et al., 1998; and Yoshikawa *et al.*, 1999, cited above). For general discussion of the procedure and benefits of the BLAST, Smith-Waterman and FASTA algorithms *see* Nicholas et al., 1998, "A Tutorial on Searching Sequence Database and Sequence Scoring Methods" [(www.psd.edu)] and references cited therein.

Paragraph replaced on Pages 36-37

In other embodiments, binding can be detected without making use of a direct or indirect label. For example, a biophysical property which alters when binding occurs can be assayed. A solid support system particularly advantageous for such screening is the BIAcore 2000™ system, available commercially from BIAcore, Inc. (Piscataway, NJ). The BIAcore™ instrument [(http://www.biacore.com)} uses the optical phenomenon of surface plasmon resonance (SPR) to monitor biospecific interactions in real-time. The SPR effect is essentially an evanescent electrical field that is affected by local changes in refractive index at a metal-liquid interface. A sensor chip made up of a sandwich of gold film between glass and a carboxymethyl dextran matrix to which the ligand or protein to be assayed is chemically linked. This sensor chip is mounted on a fluidics cartridge forming flow cells through which analyte compounds can be injected. Ligand-analyte interactions on the sensor chip are detected as changes in the angle of a beam of polarized light reflected from the chip surface. Binding of any mass to the chip affects SPR in the gold/dextran layer. This change in the electrical field in the gold layer interacts with the reflected light beam and alters the angle of reflection proportional to the amount of mass bound. Reflected light is detected on a diode array and translated to the binding signal expressed as response units (RU). As the response is directly proportional to the mass bound, kinetic and equilibrium constants for protein-protein interactions can be measured.